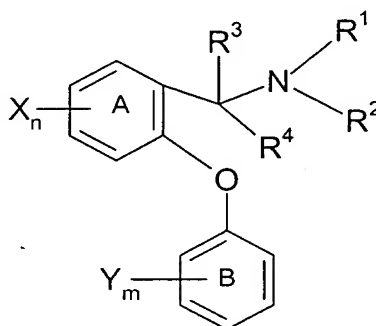


CLAIMS

1. A pharmaceutical composition for the treatment of sleep disorders including sleep apnea in a mammal, comprising: (a) a compound that exhibits activity, respectively, as an SRI antidepressant, or a pharmaceutically acceptable salt thereof; (b) a 5HT1a antagonist or an
5 alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, sleep disorders including sleep apnea depression with increased efficacy.

2. A pharmaceutical composition according to claim 1, wherein the SRI
10 antidepressant agent or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen
15 of structure I and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen (C₁-C₄)alkyl, (C₂-C₄)alkenyl,
20 and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from
25 hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to
5 three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R² and R³, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may
10 optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X and each Y is selected, independently, from hydrogen, halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino,
15 (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl wherein R⁵ is hydrogen or (C₁-C₆)alkyl, and SO_p(C₁-C₆)alkyl wherein p is zero, one or two; and

with the proviso that: (a) no more than one of NR¹R², CR³R⁴ and R²NCR³ can form a ring; and (b) at least one X must be other than hydrogen when (i) R³ and R⁴ are both hydrogen, (ii) R¹ and R² are selected, independently, from hydrogen and (C₁-C₄)alkyl, and (iii)
20 ring B is mono- or disubstituted with, respectively, one or two halo groups;
or a pharmaceutically acceptable salt thereof.

3. A compound or salt according to claim 2, wherein n is one, X is fluoro, R³ and R⁴ are hydrogen, R¹ is hydrogen, R² is methyl, m is two and Y is Y_m is 3,4-dichloro.

4. A compound or salt according to claim 2, wherein m is zero, n is one, R³ and
25 R⁴ are hydrogen, X is chloro, bromo, iodo or methyl, R¹ is hydrogen and R² is methyl.

5. A compound or salt according to claim 2, wherein said compound or salt is selected from the following compounds and their pharmaceutically acceptable salts:

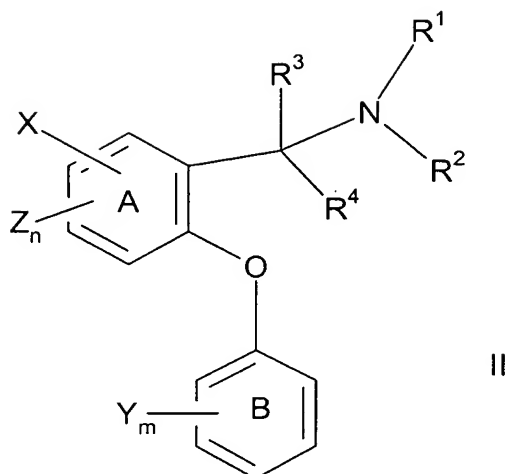
[2-(3,4-Dichlorophenoxy)-5-fluorobenzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-fluorobenzyl]-methylamine;
30 [2-(3,4-Dichlorophenoxy)-5-trifluoromethylbenzyl]-dimethylamine;
N-[4-(3,4-Dichlorophenoxy)-3-dimethylaminomethylphenyl]-acetamide;
{1-[2-(3,4-Dichlorophenoxy)phenyl]-ethyl}-dimethylamine;
[2-(3,4-Dichlorophenoxy)-4-trifluoromethylbenzyl]-dimethylamine;

- [2-(3,4-Dichlorophenoxy)-4-trifluoromethylbenzyl]-methylamine;
[4-Chloro-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine;
{1-[2-(3,4-Dichlorophenoxy)phenyl]-ethyl}-methylamine;
5 {1-[2-(4-Chlorophenoxy)phenyl]ethyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methoxybenzyl]-methylamine;
[2-(4-Chlorophenoxy)-5-fluorobenzyl]-methylamine;
{1-[2-(4-Chlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methylbenzyl]-dimethylamine;
10 [4-Bromo-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
[5-Bromo-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-4,5-dimethoxybenzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-4-methoxybenzyl]-dimethylamine;
4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-benzonitrile;
15 [2-(3,4-Dichlorophenoxy)-4,5-dimethylbenzyl]-methylamine;
3-(3,4-Dichlorophenoxy)-4-methylaminomethyl-benzonitrile;
(+)-(1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl)-methylamine;
(-)-(1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl)-methylamine;
[2-(3,4-Dichlorophenoxy)-5-trifluoromethyl-benzyl]-methylamine;
20 [2-(3,4-Dichlorophenoxy)-4-methoxybenzyl]-methylamine;
[2-(4-Chloro-3-fluorophenoxy)-5-fluorobenzyl]-methylamine;
[2-(3-Chloro-4-fluorophenoxy)-5-fluorobenzyl]-methylamine;
(+/-)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
(-)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
25 (+)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-N-methylpyrrolidine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methylethyl}-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methylethyl}-dimethylamine;
[4-Chloro-2-(4-chlorophenoxy)-5-fluorobenzyl]-methylamine;
30 [2-(3,4-Dichlorophenoxy)-5-fluoro-4-methoxybenzyl]-methylamine;
[4-(3,4-Dichlorophenoxy)-3-(dimethylaminomethyl)-phenyl]-dimethylamine
[5-Fluoro-2-(4-fluoro-3-methoxyphenoxy)-benzyl]-dimethylamine;
[2-(4-Chlorophenoxy)-5-isopropylbenzyl]-methylamine;

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{1-[2-(4-Chlorophenoxy)-5-trifluoromethylphenyl]-ethyl}-methylamine;
[2-(4-Chlorophenoxy)-4,5-dimethylbenzyl]-methylamine;
{1-[5-Chloro-2(3,4-dichlorophenoxy)phenyl]-propyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-benzyl]-methylamine;
5 {1-[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-phenyl]-ethyl}-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-phenyl]-1-methylethyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-benzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-methanesulfinyl-benzyl]-dimethylamine ;
[2-(3,4-Dichlorophenoxy)-5-methanesulfinyl-benzyl]-methylamine;
10 [2-(3,4-Dichlorophenoxy)-5-methanesulfonyl-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methanesulfonyl-benzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-(propane-2-sulfonyl)-benzyl]-methylamine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-piperidine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methyl-piperidine;
15 3-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-4-methyl-morpholine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1,2-dimethyl-piperidine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-cyclopropyl}-dimethylamine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1,5-dimethyl-pyrrolidine;
3-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-4-methyl-thiomorpholine;
20 {1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-cyclopentyl}-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-(propane-2-sulfonyl)-phenyl]-ethyl}-methylamine; and
[4-Chloro-2-(3,4-dichlorophenoxy)-5-methanesulfonyl-benzyl]-methylamine.

6. A pharmaceutical composition according to claim 1, wherein the SRI
antidepressant agent or pharmaceutically acceptable salt thereof is selected from compounds of
25 the formula II, as defined below, and their pharmaceutically acceptable salts:



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of formula II and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R² and R³, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may

optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X is selected, independently, from phenyl, heteroaryl and heterocycle, and wherein each X may be further substituted by hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, hydroxy, carbonyl, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two;

each Y is selected, independently, from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two; and

each Z is selected independently from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy; or a pharmaceutically acceptable salt thereof.

7. A compound of salt according to claim 6, wherein ring B is phenyl, not replaced with a naphthyl group.

8. A compound or salt according to claim 6, wherein each Y is hydrogen or halo.

9. A compound or salt according to claim 7, wherein m is 1 or 2, and wherein each Y is chlorine.

10. A compound or salt according to claim 6, wherein X is selected from furan, thiophene, pyrrole, and 1,2,3-triazole, and wherein X may be further substituted.

11. A compound or salt according to claim 6, wherein each Z is selected from hydrogen and halo.

12. A compound or salt according to claim 11, wherein each Z is hydrogen.

13. A compound or salt according to claim 6, wherein R³ and R⁴ are independently selected from hydrogen and unsubstituted (C₁-C₄) alkyl.

14. A compound or salt according to claim 13, wherein one or both of R³ and R⁴ are hydrogen.

15. A compound or salt according to claim 6, wherein R¹ and R² are independently selected from hydrogen and unsubstituted (C₁-C₄)alkyl.

16. A compound or salt according to claim 15, wherein one of R¹ and R² is hydrogen and the other of R¹ and R² is (C₁-C₄)alkyl.

17. A compound or salt according to claim 15, wherein one of R¹ and R² is hydrogen and the other of R¹ and R² is methyl.

5 18. A compound according to claim 6, selected from the group consisting of:

[4-(3,4-Dichlorophenoxy)-biphenyl-3-ylmethyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-thiophen-3-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-4-thiophen-3-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-4-furan-2-ylbenzyl]-methylamine;

10 [2-(3,4-Dichlorophenoxy)-5-furan-2-ylbenzyl]-methylamine;

N-[4'-(3,4-Dichlorophenoxy)-3'-methylaminomethyl-biphenyl-3-yl]-acetamide;

[2-(3,4-Dichlorophenoxy)-5-thiophen-2-ylbenzyl]-methylamine;

[4-(3,4-Dichlorophenoxy)-4'-fluoro-biphenyl-3-ylmethyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-[1,2,3]triazol-1-ylbenzyl]-methylamine;

15 [2-(3,4-Dichlorophenoxy)-5-[1,2,3]triazol-2-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-pyridin-2-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-pyridin-3-ylbenzyl]-methylamine;

1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-1H-pyrazol-3-ylamine;

[2-(3,4-Dichlorophenoxy)-5-pyridin-4-ylbenzyl]-methylamine;

20 [3-(3,4-Dichlorophenoxy)-biphenyl-4-ylmethyl]-methylamine;

[4-(3,4-Dichlorophenoxy)-4'-methyl-biphenyl-3-ylmethyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-4-thiophen-2-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-pyrimidin-2-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-pyrimidin-4-ylbenzyl]-methylamine;

25 [2-(3,4-Dichlorophenoxy)-5-(2-methylpyrimidin-4-yl)-benzyl]-methylamine;

{1-[2-(3,4-Dichlorophenoxy)-5-(2-methylpyrimidin-4-yl)-phenyl]-ethyl}-methylamine;

4-[4-(3,4-Dichlorophenoxy)-3-(1-methylpyrrolidin-2-yl)-phenyl]-2-methylpyrimidine;

[2-(4-Chlorophenoxy)-5-(1-methyl-1H-pyrrol-3-yl)-benzyl]-dimethylamine;

[5-(1-methyl-1H-pyrrol-3-yl)-2-(naphthalen-2-yloxy)-benzyl]-dimethyl amine;

30 [5-Imidazol-1-yl-2-(naphthalen-2-yloxy)-benzyl]-dimethylamine;

1,5,5-Trimethyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-imidazolidine-2,4-dione;

1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-imidazolidine-2,4-dione;

3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-thiazolidine-2,4-dione;

3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-oxazolidine-2,4-dione;

5 3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-oxazolidin-2-one;

3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-thiazolidin-2-one;

1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-imidazolidin-2-one;

1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one;

10 1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-3-methyl-tetrahydropyrimidin-2-one;

1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-3-methylimidazolidin-2-one;

3-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-thiazolidin-2-one;

3-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-oxazolidin-2-one;

15 [2-(3,4-Dichlorophenoxy)-5-(2-methylthiazol-4-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(2-methyloxazol-4-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(2,5-dimethyloxazol-4-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(2,5-dimethylthiazol-4-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,4]thiadiazol-3-yl)-benzyl]-methylamine;

20 [2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-[1,2,3]oxadiazol-4-yl-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,3]thiadiazol-4-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(2,4-dimethyloxazol-5-yl)-benzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(2,4-dimethylthiazol-5-yl)-benzyl]-methylamine;

25 [2-(3,4-Dichlorophenoxy)-5-[1,2,4]triazol-1-ylbenzyl]-methylamine;

[2-(3,4-Dichlorophenoxy)-5-(3-methyl-[1,2,4]triazol-1-yl)-benzyl]-methylamine;

[2-(4-Chlorophenoxy)-5-(3,5-dimethyl-[1,2,4]triazol-1-yl)-benzyl]-methylamine;

[2-(4-Chlorophenoxy)-5-tetrazol-1-ylbenzyl]-methylamine;

[2-(4-Chlorophenoxy)-5-(5-methyltetrazol-1-yl)-benzyl]-dimethylamine;

30 [2-(4-Chlorophenoxy)-5-[1,2,4]triazol-4-ylbenzyl]-dimethylamine;

[2-(4-Chlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-benzyl]-dimethylamine; and

{1-[2-(3,4-Dichlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-phenyl]-ethyl}-dimethylamine.

19. A pharmaceutical composition according to claim 1 wherein a 5HT1a antagonist or an alpha-2-adrenergic antagonist or a pharmaceutically acceptable salt thereof is selected from:

- (S)-(-)-pindolol [(S)-1-(1H-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol]
- 5 NAN-190 [1-(2-methoxyphenyl)-4-(4-phthalimidobutyl)piperazine]
- WAY-100635 [N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)-cyclohexanecarboxamide]
- 3-(cyclopentylpropylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide,
- robalzotan [(3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carbox-
- 10 amide]
- mirtazapine [1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine]
- Idazoxan [2-(2,3-dihydro-1,4-benzodioxin-2-yl)-4,5-dihydro-1H-imidazole hydrochloride]
- 15 delaquamine [[8aR-(8a α ,12a α ,13a α)]-5,8,8a,9,10,11,12,12a,13,13a-decahydro-3-methoxy-12-(methylsulfonyl)-6H-isoquino[2,1-g][1,6]naphthyridine]
- BRL-44408 [2-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole]
- imiloxan [2-(1-ethyl-2-imidazolyl)methyl-1,4-benzodioxan]

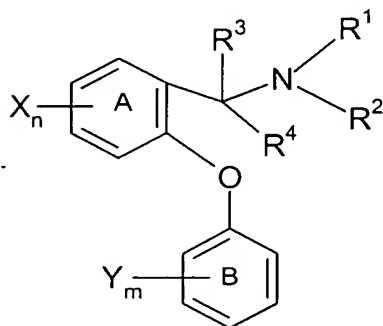
20 20. A pharmaceutical composition according to claim 1 wherein the amount of the (SRI) antidepressant, or pharmaceutically acceptable salt thereof, in said composition is from about 0.05 mg to about 1500 mg and the amount of the 5HT1a antagonist or an alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof is from about 1.0 mg to about 100 mg.

25 21. A pharmaceutical composition according to claim 20 wherein the amount of the (SRI antidepressant, or pharmaceutically acceptable salt thereof, in said composition is from about 2.5 mg to about 500 mg and the amount of the 5HT1a antagonist or an alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof is from about 1.0 mg to about 50 mg.

30 22. A method of treating sleep disorder including sleep apnea in a mammal, comprising administering to said mammal: (a) a compound that exhibits activity as an SRI antidepressant, or a pharmaceutically acceptable salt thereof; and (b) a 5HT1a antagonist or an alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof; wherein the active

agents "a" and "b" above are present in amounts that render the combination of the two agents effective in treating, respectively, sleep disorder with increased efficacy.

23. The method according to claim 22, wherein the antidepressant or SRI pharmaceutically acceptable salt thereof is selected from compounds of the formula I,



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of structure I and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R² and R³, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom,

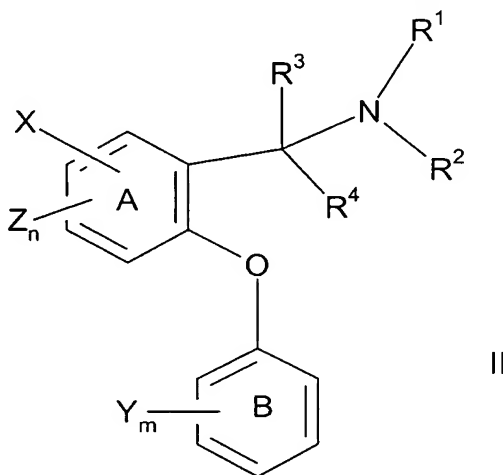
when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X and each Y is selected, independently, from hydrogen, halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl wherein R⁵ is hydrogen or (C₁-C₆)alkyl, and SO_p(C₁-C₆)alkyl wherein p is zero, one or two; and

with the proviso that: (a) no more than one of NR¹R², CR³R⁴ and R²NCR³ can form a ring; and (b) at least one X must be other than hydrogen when (i) R³ and R⁴ are both hydrogen, (ii) R¹ and R² are selected, independently, from hydrogen and (C₁-C₄)alkyl, and (iii) ring B is mono- or disubstituted with, respectively, one or two halo groups;

or a pharmaceutically acceptable salt thereof.

24. The method according to claim 22, wherein the SRI antidepressant or pharmaceutically acceptable salt thereof is selected from compounds of the formula II,



wherein phenyl ring A and phenyl ring B can each, independently, be replaced by a naphthyl group, and wherein when phenyl ring A is replaced by a naphthyl group, the ethereal oxygen of structure I and the carbon to which R³, R⁴ and NR¹R² are attached, are attached to adjacent ring carbon atoms of the naphthyl group and neither of said adjacent ring carbon atoms is also adjacent to a fused ring carbon atom of said naphthyl group;

n and m are, selected, independently, from one, two and three;

R¹ and R² are selected, independently, from hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, and (C₂-C₄)alkynyl, or R¹ and R², together with the nitrogen to which they are attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R¹ and R² are attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

R³ and R⁴ are selected, independently, from hydrogen and (C₁-C₄) alkyl optionally substituted with from one to three fluorine atoms, or R³ and R⁴, together with the carbon to which they are attached, form a four to eight membered saturated carbocyclic ring, and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

or R² and R³, together with the nitrogen to which R² is attached and the carbon to which R³ is attached, form a four to eight membered saturated ring containing one or two heteroatoms, including the nitrogen to which R² is attached, wherein the second heteroatom, when present, is selected from oxygen, nitrogen and sulfur; and wherein said ring may optionally be substituted at available binding sites with from one to three substituents selected, independently, from hydroxy and (C₁-C₆)alkyl;

each X is selected, independently, from phenyl, heteroaryl and heterocycle, and wherein each X may be further substituted by hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, hydroxy, carbonyl, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two;

each Y is selected, independently, from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy optionally substituted with from one to three fluorine atoms, cyano, nitro, amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, NR⁵(C=O)(C₁-C₄)alkyl, SO₂NR⁵R⁶ and SO_p(C₁-C₆)alkyl, wherein R⁵ and R⁶ are selected, independently, from hydrogen and (C₁-C₆)alkyl, and p is zero, one or two; and

each Z is selected independently from hydrogen, halo, (C₁-C₄)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₄)alkoxy;

or a pharmaceutically acceptable salt thereof.

25. The method according to claim 22, wherein the SRI antidepressant or pharmaceutically acceptable salt thereof, and the 5HT1a antagonist or an alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof, are administered as part of the same dosage form.

5 26. The method according to claim 22, wherein the 5HT1a antagonist or an alpha-2-adrenergic antagonist or pharmaceutically acceptable salt thereof, is administered in an amount from about 1.0 mg per day to about 100 mg per day, and the SRI antidepressant, or pharmaceutically acceptable salt thereof, is administered in an amount from about 0.05 mg day to about 1500 mg per day.

10 27. The method according to claim 22, wherein the 5HT1a antagonist or an alpha-2-adrenergic antagonist is administered in an amount ranging from about 1 mg per day to about 100 mg per day and the SRI is administered in an amount ranging from about 1.0 mg per day to 50 mg per day.

15 28. The method according to claim 22, wherein the 5HT1a antagonist or an alpha-2-adrenergic antagonist pharmaceutically acceptable salt thereof is selected from:

(S)-(-)-pindolol [(S)-1-(1H-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol];

NAN-190 [1-(2-methoxyphenyl)-4-(4-phthalimidobutyl)piperazine];

WAY-100635 [N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)-cyclohexanecarboxamide];

20 3-(cyclopentylpropylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide;

robalzotan [(3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide];

mirtazapine [1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine];

25 idazoxan [2-(2,3-dihydro-1,4-benzodioxin-2-yl)-4,5-dihydro-1H-imidazole hydrochloride];

delaquamine [[8aR-(8a α ,12a α ,13a α)]-5,8,8a,9,10,11,12,12a,13,13a-decahydro-3-methoxy-12-(methylsulfonyl)-6H-isoquino[2,1-g][1,6]naphthyridine];

30 BRL-44408 [2-[(4,5-dihydro-1H-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1H-isoindole; and

imiloxan [2-(1-ethyl-2-imidazolyl)methyl-1,4-benzodioxan];

29. The method according to claim 24, wherein the SRI antidepressant agent or pharmaceutically acceptable salt thereof that is employed in such composition is selected from the following compounds and their pharmaceutically acceptable salts:

- 5 [4-(3,4-Dichlorophenoxy)-biphenyl-3-ylmethyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-thiophen-3-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-4-thiophen-3-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-4-furan-2-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-furan-2-ylbenzyl]-methylaniline;
N-[4'-(3,4-Dichlorophenoxy)-3'-methylaminomethyl-biphenyl-3-yl]-acetamide;
10 [2-(3,4-Dichlorophenoxy)-5-thiophen-2-ylbenzyl]-methylaniline;
[4-(3,4-Dichlorophenoxy)-4'-fluoro-biphenyl-3-ylmethyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-[1,2,3]triazol-1-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-[1,2,3]triazol-2-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-pyridin-2-ylbenzyl]-methylaniline;
15 [2-(3,4-Dichlorophenoxy)-5-pyridin-3-ylbenzyl]-methylaniline;
1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethylphenyl]-1H-pyrazol-3-ylamine;
[2-(3,4-Dichlorophenoxy)-5-pyridin-4-ylbenzyl]-methylaniline;
[3-(3,4-Dichlorophenoxy)-biphenyl-4-ylmethyl]-methylaniline;
[4-(3,4-Dichlorophenoxy)-4'-methyl-biphenyl-3-ylmethyl]-methylaniline;
20 [2-(3,4-Dichlorophenoxy)-4-thiophen-2-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-pyrimidin-2-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-pyrimidin-4-ylbenzyl]-methylaniline;
[2-(3,4-Dichlorophenoxy)-5-(2-methylpyrimidin-4-yl)-benzyl]-methylaniline;
{1-[2-(3,4-Dichlorophenoxy)-5-(2-methylpyrimidin-4-yl)-phenyl]-ethyl}-methylaniline;
25 4-[4-(3,4-Dichlorophenoxy)-3-(1-methylpyrrolidin-2-yl)-phenyl]-2-methylpyrimidine;
[2-(4-Chlorophenoxy)-5-(1-methyl-1H-pyrrol-3-yl)-benzyl]-dimethylaniline;
[5-(1-methyl-1H-pyrrol-3-yl)-2-(naphthalen-2-yloxy)-benzyl]-dimethyl amine;
[5-Imidazol-1-yl-2-(naphthalen-2-yloxy)-benzyl]-dimethylaniline;
1,5,5-Trimethyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-
30 imidazolidine-2,4-dione;
1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-imidazolidine-2,4-
dione;
3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-thiazolidine-2,4-dione;

- 3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-oxazolidine-2,4-dione;
3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-oxazolidin-2-one;
3-[3-Methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-thiazolidin-2-one;
1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-imidazolidin-2-one;
5 1-Methyl-3-[3-methylaminomethyl-4-(naphthalen-2-yloxy)-phenyl]-tetrahydro-
pyrimidin-2-one;
1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-3-methyl-
tetrahydropyrimidin-2-one;
1-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-3-methylimidazolidin-2-one;
10 3-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-thiazolidin-2-one;
3-[4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-phenyl]-oxazolidin-2-one;
[2-(3,4-Dichlorophenoxy)-5-(2-methylthiazol-4-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(2-methyloxazol-4-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(2,5-dimethyloxazol-4-yl)-benzyl]-methylamine;
15 [2-(3,4-Dichlorophenoxy)-5-(2,5-dimethylthiazol-4-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,4]thiadiazol-3-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-[1,2,3]oxadiazol-4-yl-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(5-methyl-[1,2,3]thiadiazol-4-yl)-benzyl]-methylamine;
20 [2-(3,4-Dichlorophenoxy)-5-(2,4-dimethyloxazol-5-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(2,4-dimethylthiazol-5-yl)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-[1,2,4]triazol-1-ylbenzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-(3-methyl-[1,2,4]triazol-1-yl)-benzyl]-methylamine;
[2-(4-Chlorophenoxy)-5-(3,5-dimethyl-[1,2,4]triazol-1-yl)-benzyl]-methylamine;
25 [2-(4-Chlorophenoxy)-5-tetrazol-1-ylbenzyl]-methylamine;
[2-(4-Chlorophenoxy)-5-(5-methyltetrazol-1-yl)-benzyl]-dimethylamine;
[2-(4-Chlorophenoxy)-5-[1,2,4]triazol-4-ylbenzyl]-dimethylamine;
[2-(4-Chlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-benzyl]-dimethylamine; and
{1-[2-(3,4-Dichlorophenoxy)-5-(1-methyl-1H-tetrazol-5-yl)-phenyl]-ethyl}-
30 dimethylamine.

30. The method according to claim 23, wherein the antidepressant or pharmaceutically acceptable salt thereof that is employed in such method is selected from the following compounds and their pharmaceutically acceptable salts:

- [2-(3,4-Dichlorophenoxy)-5-fluorobenzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-fluorobenzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-trifluoromethylbenzyl]-dimethylamine;
N-[4-(3,4-Dichlorophenoxy)-3-dimethylaminomethylphenyl]-acetamide;
5 1-[2-(3,4-Dichlorophenoxy)phenyl]-ethyl}-dimethylamine;
[2-(3,4-Dichlorophenoxy)-4-trifluoromethylbenzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-4-trifluoromethylbenzyl]-methylamine;
[4-Chloro-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine;
10 {1-[2-(3,4-Dichlorophenoxy)phenyl]-ethyl}-methylamine;
{1-[2-(4-Chlorophenoxy)phenyl]ethyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methoxybenzyl]-methylamine;
[2-(4-Chlorophenoxy)-5-fluorobenzyl]-methylamine;
{1-[2-(4-Chlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine.
15 [2-(3,4-Dichlorophenoxy)-5-methylbenzyl]-dimethylamine;
[4-Bromo-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
[5-Bromo-2-(3,4-dichlorophenoxy)-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-4,5-dimethoxybenzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-4-methoxybenzyl]-dimethylamine;
20 4-(3,4-Dichlorophenoxy)-3-methylaminomethyl-benzonitrile;
[2-(3,4-Dichlorophenoxy)-4,5-dimethylbenzyl]-methylamine;
3-(3,4-Dichlorophenoxy)-4-methylaminomethyl-benzonitrile;
(+)-{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine;
(-)-{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-ethyl}-methylamine;
25 [2-(3,4-Dichlorophenoxy)-5-trifluoromethyl-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-4-methoxybenzyl]-methylamine;
[2-(4-Chloro-3-fluorophenoxy)-5-fluorobenzyl]-methylamine;
[2-(3-Chloro-4-fluorophenoxy)-5-fluorobenzyl]-methylamine;
(+/-)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
30 (-)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
(+)-2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-pyrrolidine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-N-methylpyrrolidine.
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methylethyl}-methylamine;

{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methylethyl}-dimethylamine;
[4-Chloro-2-(4-chlorophenoxy)-5-fluorobenzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-fluoro-4-methoxybenzyl]-methylamine;
[4-(3,4-Dichlorophenoxy)-3-(dimethylaminomethyl)-phenyl]-dimethylamine
5 [5-Fluoro-2-(4-fluoro-3-methoxyphenoxy)-benzyl]-dimethylamine;
[2-(4-Chlorophenoxy)-5-isopropylbenzyl]-methylamine;
{1-[2-(4-Chlorophenoxy)-5-trifluoromethylphenyl]-ethyl}-methylamine;
[2-(4-Chlorophenoxy)-4,5-dimethylbenzyl]-methylamine;
{1-[5-Chloro-2(3,4-dichlorophenoxy)phenyl]-propyl}-methylamine;
10 [2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-benzyl]-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-phenyl]-ethyl}-methylamine;
{1-[2-(3,4-Dichloro-phenoxy)-5-methylsulfanyl-phenyl]-1-methylethyl}-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methylsulfanyl-benzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-methanesulfinyl-benzyl]-dimethylamine ;
15 [2-(3,4-Dichlorophenoxy)-5-methanesulfinyl-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methanesulfonyl-benzyl]-methylamine;
[2-(3,4-Dichlorophenoxy)-5-methanesulfonyl-benzyl]-dimethylamine;
[2-(3,4-Dichlorophenoxy)-5-(propane-2-sulfonyl)-benzyl]-methylamine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-piperidine;
20 2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1-methyl-piperidine;
3-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-4-methyl-morpholine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1,2-dimethyl-piperidine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-cyclopropyl}-dimethylamine;
2-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-1,5-dimethyl-pyrrolidine;
25 3-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-4-methyl-thiomorpholine;
{1-[2-(3,4-Dichlorophenoxy)-5-fluorophenyl]-cyclopentyl}-methylamine;
{1-[2-(3,4-Dichlorophenoxy)-5-(propane-2-sulfonyl)-phenyl]-ethyl}-methylamine; and
[4-Chloro-2-(3,4-dichlorophenoxy)-5-methanesulfonyl-benzyl]-methylamine.